2013-1342

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BUTAMAX(TM) ADVANCED BIOFUELS LLC,

Plaintiff-Appellant,

v.

GEVO, INC.

Defendant-Appellee.

Appeal from the United States District Court for the
District of Delaware in No. 11-CV-0054, Judge Sue L. Robinson

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APPELLEE'S RESPONSIVE BRIEF

NON-CONFIDENTIAL VERSION

CORRECTED

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CERTIFICATE OF INTEREST

Counsel for Defendant-Appellee Gevo, Inc. certifies the following:

1. The full name of every party or amicus represented by me is: Gevo, Inc.

2. The name of the real party in interest (if the party named in the caption is not the real party in interest) represented by me is: None.

3. All parent corporations and any publicly held companies that own 10 percent or more of the stock of the party or amicus curiae represented by me are: None.

4. The names of all law firms and the partners or associates that appeared for the party or amicus now represented by me in the trial court or agency or are expected to appear in this court are:

   Cooley LLP: Stephen C. Neal, James P. Brogan, Michelle S. Rhyu, Lori R. Mason, Benjamin G. Damstedt, Daniel J. Knauss, Adam Pivovar, Carolyn V. Juarez, Tryn Stimart, Jesse Dyer, Ann Marie Byers

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July 15, 2013 */s/ Michelle S. Rhyu*

Michelle S. Rhyu

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CONFIDENTIAL MATERIAL OMITTED

Confidential material has been omitted from pages 2, 27, 39 and 40 of this Opening Brief. That information relates to the subject matter of the Preliminary Statement Section I; Summary of the Argument Section V, and Argument Section VII.A.3.a and contains excerpts from documents produced by Plaintiff-Appellant Butamax, Inc., designated as confidential by Plaintiff-Appellant Butamax, Inc., and filed under seal with the district court pursuant to the Protective Order entered on July 18, 2011.

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STATEMENT OF RELATED CASES

An earlier appeal was taken from the district court's denial of Butamax Advanced Biofuels LLC's ("Butamax's") motion for a preliminary injunction against Gevo Inc., ("Gevo"), before Chief Judge Rader, and Circuit Judges Dyk and Wallach, with a decision issuing on Nov. 16, 2012. *Butamax(TM) Advanced Biofuels LLC v. Gevo, Inc.*, 486 F. App'x 883, 883 (Fed. Cir. 2012).

The patents at issue in this appeal are U.S. Patent No. 7,993,889 (the "'889 patent), which is subject to a pending *inter partes* reexamination, No. 95/001,735 and a pending *ex parte* reexamination, No. 90/012,503, and U.S. Patent No. 7,851,188 (the "'188 patent), which is also subject to a pending *inter partes* reexamination, No. 95/001,857.

A continuation of the '188 and '889 patents (collectively the "Butamax Patents"), U.S. Patent No. 8,178,328, is in suit in *Butamax(TM) Advanced Biofuels LLC v. Gevo, Inc.*, Civil Action No. 12-602-SLR (D. Del.). A continuation of the '188 and '889 patents, U.S. Patent No. 8,283,144, is in suit in *Butamax(TM) Advanced Biofuels LLC v. Gevo, Inc.*, Civil Action No. 12-1300-SLR (D. Del.). A continuation-in-part of the '188 and '889 patents, U.S. Patent No. 8,273,558, is in suit in *Butamax(TM) Advanced Biofuels LLC v. Gevo, Inc.*, Civil Action No. 12-1200-SLR (D. Del.). Counsel for Gevo is not aware of any other case pending in

this or any other court that will directly affect or be directly affected by this Court's decision in this appeal.

STATEMENT OF JURISDICTION

Gevo does not disagree with Appellant's Statement of Jurisdiction.

I. PRELIMINARY STATEMENT

Butamax has spent over two years of the parties' and the courts' time and resources running from its own clear, limiting definition of the key disputed term at the center of this dispute. The claim construction issue presented on appeal turns on which electron donor the "acetohydroxy acid isomeroreductase" ("AAIR") enzyme uses. The patent itself clearly and unequivocally limits that donor to an "NAD**P**H" molecule, expressly defining AAIR enzymes as "using NAD**P**H."

Unwilling to accept the hard truth that the accused Gevo enzyme uses a different molecule, "NADH," Butamax tries to rewrite history. On appeal, Butamax asserts that the claims should cover any "enzyme that catalyzes the conversion of AL to DHIV," not just enzymes that use NAD**P**H.[1] Butamax's construction flouts basic rules of claim construction. The patents expressly define "AAIR" as limited to enzymes "using NAD**P**H."[2] Moreover, in response to repeated rejections under section 112, Butamax added the AAIR limitation to the claims and told the Patent Office that the amended claims covered only the "specific enzymes" described and defined in the specification.[3]

---

[1] Brief for Plaintiff-Appellant Butamax(TM) Advanced Biofuels LLC ("BM Br.") at 34.
[2] '188 patent, 7:35-50.
[3] A7142; A7583.

CONFIDENTIAL INFORMATION REDACTED

Butamax also mistakenly attacks the district court's construction—which correctly limits the AAIR term to "NADPH dependent" enzymes—as unsupported and unscientific. (A9535-36 ("[T]here's nothing in the specification or the prosecution history that says NAD**P**H-dependent."); A9540 ("But enzymes don't prefer.").) These litigation-driven contentions flatly contradict the record. The patents-in-suit use the term "NAD**P**H-dependent,"[4] Butamax's internal documents regularly apply the terms "dependent" and "prefers" to NAD**P**H and NADH,[5] and Butamax's own public patent applications apply the terms.[6]

As a back-up position, Butamax also claims that any detectable "use" of NADPH, no matter how small, suffices to come within the claim scope. Butamax's Arfin argument ignores an undisputed scientific reality: all known enzymes that have activity with NAD**P**H also have at least small, detectable amounts of activity with NADH, and vice-versa. Because Butamax's proposed back-up construction sets the threshold for "use" so low, it would render meaningless the patents' careful distinctions between enzymes that "use NAD**P**H,"

[4] '188 patent, 4:60-62 ("*NADPH-dependent* cinnamyl alcohol dehydrogenase") (emphasis added).

[redacted]

[6] A8794, A8803, ¶ 7 ("strictly *NADPH-dependent* p-Hydroxybenzoate hydroxylase (PHBH)"); *id.*, ¶ 134 ("*NADPH-dependent* reductase, YqhD") (emphasis added).

those that "use NAD[H]," and those that allow "utilizing NADH ... and/or NAD**P**H."[7] Under Butamax's construction, those defined enzymes would each use both NADPH and NADH.

Resolving this "AAIR" claim construction dispute requires affirmance of no literal infringement. It also requires affirmance of the summary judgment of noninfringement under the doctrine of equivalents, because the doctrines of vitiation and prosecution history estoppel bar Butamax's equivalents theory.

The other main issue on appeal is invalidity for insufficient written description. Claims 12 and 13 of the '889 patent relate to inactivating genes used for pathways that compete with isobutanol production. But the snippets cited by Butamax from the '889 patent contain nothing permitting a factfinder to conclude that the patentees possessed anything other than a wish or research plan, which fails this Court's section 112 standard.

II. COUNTER-STATEMENT OF THE ISSUES

1. Whether the district court correctly construed the term "acetohydroxy acid isomeroreductase" as limited to "NADPH-dependent" enzymes based on the intrinsic record, including the patents' express definition.

[7] '188 patent, 7:35-40, 8:14-16, 8:25-29.

2. Whether the district court correctly rejected Butamax's reliance on extrinsic evidence that contradicted the intrinsic record and the overall weight of the scientific record.

3. Whether this Court should affirm the summary judgment of noninfringement under the doctrine of equivalents, where Gevo's NADH-dependent enzymes are substantially different from Butamax's claimed NADPH-dependent enzymes and prosecution history estoppel bars Butamax's equivalents theory.

4. Whether the district court correctly granted summary judgment of invalidity for insufficient written description where the only alleged support for the two claims at-issue was nothing more than a wish or research plan.

III. COUNTER-STATEMENT OF THE CASE

Gevo agrees that Butamax has identified the decisions relevant to this appeal. As detailed below in the Counter-Statement of the Facts, Butamax's argumentative Statement of the Case incorrectly describes the record, the parties' positions, and the district court's reasoning and decision.

IV. COUNTER-STATEMENT OF THE FACTS

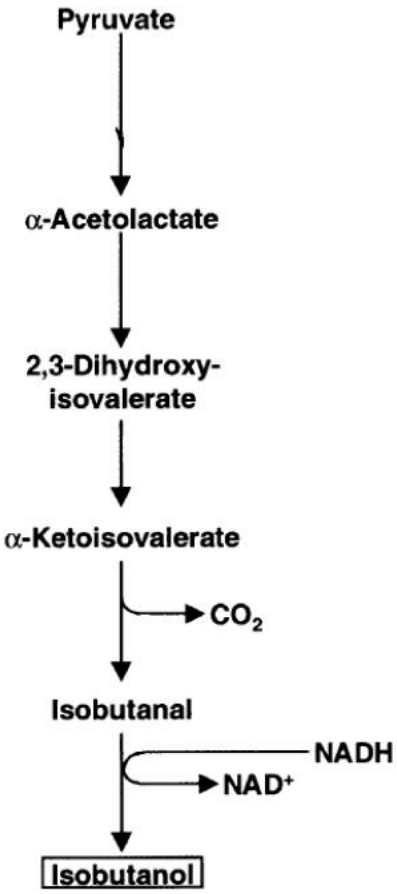
A. The Steps of the Isobutanol Pathway and the Enzymes Used in Performing the Steps Have Long Been Known.

1. The five-step isobutanol pathway was known.

People have made alcohols for thousands of years using microorganisms like yeast. (A17954-55 at ¶ 20.) Microorganisms naturally consume sugars and produce alcohols, including drinking alcohol and "fusel alcohols" like isobutanol. (A17953-55 at ¶¶ 19-21.) Microorganisms transform sugars into alcohols through a series of chemical reactions called a "pathway." (A17954-56 at ¶¶ 20-23.) The ingredients for the pathway steps are called "substrates." (A18251.)

The primary pathway for producing isobutanol was well-known long before the mid-2000s. (*See generally* A17954-91 at ¶¶ 20-83.) A 2001 textbook written by Boulton summarized the isobutanol pathway, which begins with pyruvate and proceeds through five steps to produce isobutanol[8]:

[8] "Isobutanal" is also known as "isobutyraldehyde." (A17954-55 at ¶ 20.)



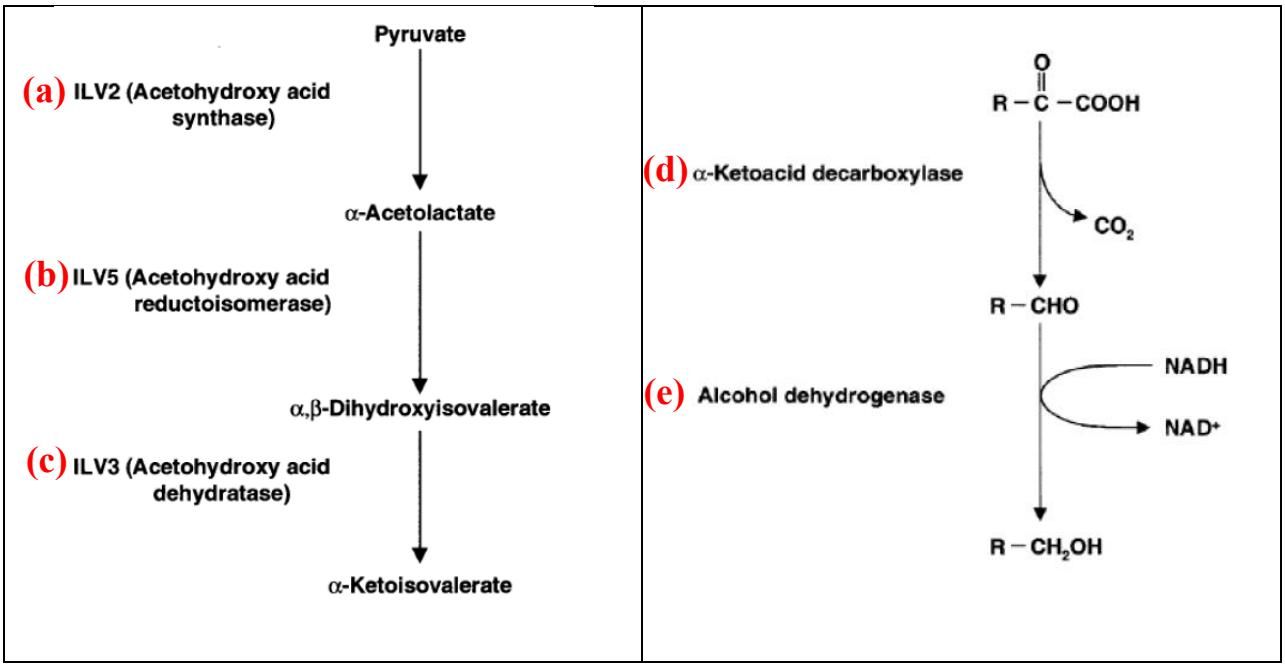
(A17963-66 at ¶¶ 37-40 (depicting A17879, Fig. 3.14 (excerpted for clarity)); A17875, Fig. 3.11 (pyruvate is produced from sugars).) Boulton's description of the pathway builds on research by Webb, Yoshizawa, Chen, and many others going back to the 1960s showing the same five steps. (A17954-63 at ¶¶ 20-36.)

2. Enzymes for catalyzing each step were known.

The isobutanol pathway takes place in cells that contain vast numbers of different types of molecules colliding into each other due to random thermal movements. (A18249.) Special molecules called enzymes dramatically speed up reactions or allow them to occur at all: "[E]nzymes are remarkable molecules that

determine all the chemical transformations that make and break covalent bonds in cells." (A18251.) Enzymes convert substrates "into one or more chemically modified products, doing this over and over again with amazing rapidity." (*Id.*) "Enzymes speed up reactions, often by a factor of a million or more, without themselves being changed." (*Id.*) This "catalysis of organized sets of chemical reactions by enzymes ... creates and maintains the cell, making life possible." (*Id.*) Enzymes perform these critical functions through their structural features, including their three-dimensional shape and charge. (A10151-52 at ¶ 16.) Enzyme structures are highly specialized to promote specific reactions using specific substrates. (A18275-76; A10154-55 at ¶ 21.)

The enzymes used in the isobutanol pathway were well-characterized before the mid-2000s. ('188 Patent, 7:40-50 ("sequences are available from a vast array of microorganisms"); *id.*, 7:24-34, 7:53-62, 7:65-8:8, 8:11-24; 19:50-55; A17995-99, A18010 at ¶¶ 93, 96, 98, 100, 124.) The annotated figures below from Boulton show the enzymes that catalyze the five steps.



(A17964-65 at ¶¶ 38-39 (citing Figs. 3.21, 3.13).)

Techniques for metabolic engineering were also widely available by the mid-2000s. (A17986-87 at ¶¶ 76-78.) These techniques allow people to make copies of natural enzymes so as to "increase the flux through the pathway." (A17995 at ¶ 93 (citing A17890); A17881.) Before Butamax, scientists including Yocum and Larroy had applied these techniques to create bioengineered yeast that produced isobutanol and expressed "heterologous"[9] copies of enzymes in the isobutanol pathway. (A18014-19 at ¶¶ 133-40.)

[9] The patents define a "'foreign gene' or 'heterologous gene' [as] a gene not normally found in the host organism, but that is introduced into the host organism by gene transfer." ('188 patent, 10:10-16.)

3. The natural isobutanol pathway is imbalanced, resulting in little isobutanol production.

a. The natural pathway uses NADPH for one reaction step and NADH for another reaction step.

The key reaction for this appeal is the second step of the natural pathway, which converts acetolactate ("AL") to 2,3-dihydroxy-isovalerate ("DHIV"). An enzyme called "acetohydroxy acid isomeroreductase" ("AAIR") catalyzes this step. AAIR enzymes are a subset of enzymes in a broader category of "ketol acid reductoisomerase" ("KARI") enzymes. (A18332, 63:20-23.) Acetohydroxy acid *isomeroreductase* involves both isomerization—rearranging the substrate without adding any new atoms—and reduction—adding an electron to the substrate. (A18280; A10151-52 at ¶ 16.)

Reduction requires a "cofactor" or "coenzyme" that donates an electron to the reaction. (A10152 at ¶ 17.) Two molecules called NADPH and NADH are fundamental molecules used by all life to donate and accept electrons. (A17797-99 at ¶¶ 9-13; A18247-48.) In their "reduced" forms (NADPH and NADH), they act as electron donors, providing a hydrogen atom and its electron to the substrate. (*Id.*) In their "oxidized" forms (NADP+ and NAD+), they act as electron acceptors, receiving a hydrogen atom and its electron from the substrate.[10] (*Id.*)

[10] The "+" in "NADP+" and "NAD+" indicates that the molecules have donated their electron and are in their oxidized, positively charged states.

Although NADPH and NADH have a "close chemical resemblance," they are "not metabolically interchangeable." (A18300.) NADPH is used predominantly in "reductive biosynthetic reactions," which make more complex molecules from simpler molecules. (A18248; A17815-16 at ¶ 41.) NADH, in contrast, is used predominantly in "oxidative degradation" reactions, which break down complex molecules. (A10166 at ¶ 38.) For organisms to survive, they must limit competition between the oxidative and reductive pathways. (*Id.*) "The difference of a single phosphate group has no effect on the electron-transfer properties of NADPH compared with NADH, but *it is crucial for their distinctive roles*." (A18247-48 (emphasis added).[11]) An enzyme that prefers using NADPH over NADH is called an "NADPH-dependent" enzyme. (A10167-68 at ¶¶ 39-40, 42; A16-19.)

The isobutanol pathway provides a striking example of how natural selection has used the chemical differences between NADPH and NADH to differentiate enzymes. Both the natural isobutanol pathway and Butamax's claimed pathway include reduction reactions at the second and fifth steps. For the second step, the

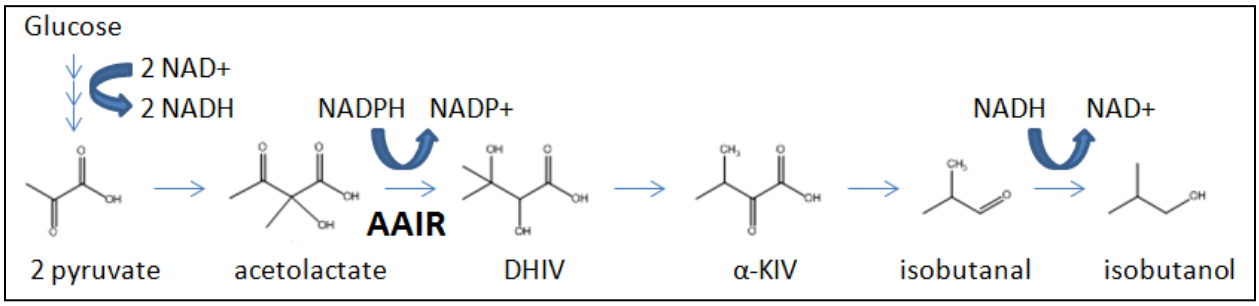
[11] A18300 ("[E]nzymes involved in oxidative and reductive metabolism exhibit a high degree of specificity toward their respective coenzymes."); A18292 (enzymes distinguish cofactors by "possession of the extra phosphate group by NADP+ ... a simple yet impressive example of the power of molecular recognition in biochemical reactions"); A18247-48 (NADPH and NADH "are independently regulated, so that the cell can independently adjust the supply of electrons for these two contrasting purposes").

pathways employ an enzyme that strongly prefers NADPH as the cofactor. (A10164-66 at ¶¶ 36-38.) For the fifth step, they employ an enzyme that strongly prefers NADH as the cofactor. (A17892.)

Natural selection, however, has not created any enzymes that select perfectly for NADPH or NADH. (A17815 at ¶ 39.) Accordingly, as Butamax admits, all nicotinamide-related enzymes have at least some detectable activity with both NADPH and NADH. (A18324, 22:12-20 (Butamax inventor Maggio-Hall—"I don't think enzymes exist in nature that can't use the other one to some extent."); A18326 & A18328, 148:20-24, 149:16-21, 169:11-170:11 (Butamax employee Nelson—all wild type and engineered KARIs he knows of "use both NADH and NADPH").)

b. The natural pathway creates an excess of NADH and a shortage of NADPH.

As shown below, the precursor reaction to the isobutanol pathway—the conversion of glucose to pyruvate—creates two NADH molecules but the isobutanol pathway uses only one NADH molecule:



(A18303 at ¶ 27; A10188 at ¶ 84.) Because the natural isobutanol pathway uses an NADPH-dependent enzyme for the second step, cycling through the pathway repeatedly creates many extra molecules of NADH and requires many extra molecules of NADPH to be found from elsewhere. This imbalance severely limits yield and, as a result, the natural pathway produces little isobutanol. (*Id*.) This imbalance has especially severe consequences in anaerobic conditions, where NADPH is scarce. (A18269, 41:10-60; A18255.)

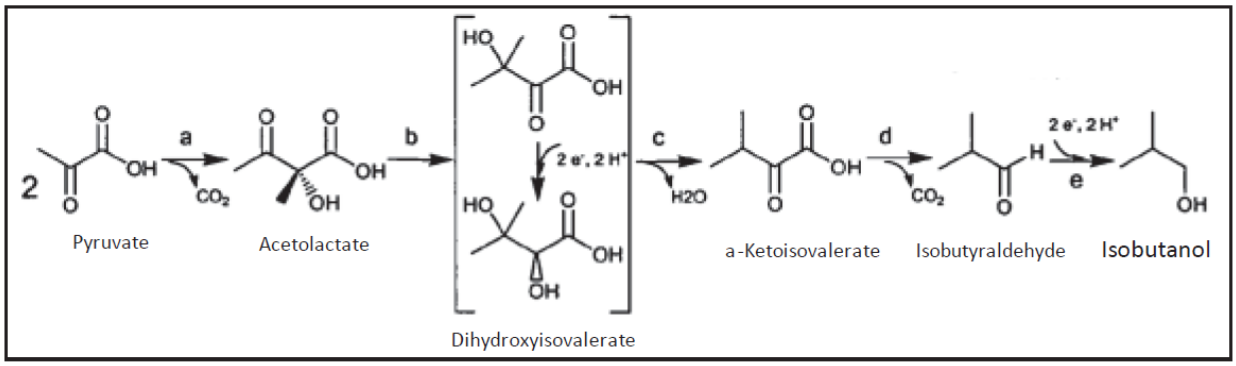
B. The Asserted Patents Claim the Use of the Known Enzymes in the Known Isobutanol Pathway.

1. Butamax's purported invention employs the known isobutanol pathway and enzymes, with similarly low production of isobutanol.

Butanol is a widely used chemical, with "an energy content similar to that of gasoline." ('188 patent, 1:20-25, 6:60-63.) The patents assert that chemically synthesizing one form of butanol, isobutanol, is "generally expensive and not environmentally friendly," but producing isobutanol "from plant-derived raw materials would minimize green house gas emissions." (*Id.*, 1:32-37.)

The Butamax patents recognize that "[i]sobutanol is produced biologically as a by-product of yeast fermentation." (*Id.*, 1:39-40.) During this natural process, however, "[y]ields of fusel oil and/or its components ... are typically low." (*Id.*, 1:47-50.)

Although the Butamax patents purport to create an "engineered isobutanol biosynthetic pathway" (*id.*, 2:3-4), they duplicate the steps from the natural isobutanol pathway:



(BM Br. at 11 (annotations in Butamax's brief); A17969-70 at ¶¶ 47-50.) The patents concede that the recited pathway uses the "well-characterized pathways for valine biosynthesis ... and valine catabolism." ('188 patent, 12:19-22.) The patents likewise point only to known enzymes and known DNA sequences for encoding the enzymes. (*E.g.*, *id.*, 7:35-50 (citing GenBank sequence references).) The patents also admit that techniques for copying these known DNA sequences and enzymes were routine. (*Id.*, 11:34-35 ("Standard recombinant DNA and molecular cloning techniques used herein are well-known in the art ...."); *id.*, 19:45-49, 20:19-22.)

Because Butamax's purported invention employed the known enzymes for use in the known pathway, it obtained essentially the same results: low isobutanol yields. (A00048; A10107; A18339; A18038 at ¶ 189.)

2. The Butamax patents define the AAIR enzyme as NADPH-dependent and distinguish it from other enzymes.

Butamax expressly defined the enzyme in the patent as NADPH-dependent:

> The terms "acetohydroxy acid isomeroreductase" and "acetohydroxy acid reductoisomerase" are used interchangeably herein to refer to an enzyme that catalyzes the conversion of acetolactate to 2,3-dihydroxyisovalerate ***using NADPH*** (reduced nicotinamide adenine dinucleotide phosphate) as an electron donor.

('188 patent, 7:35-50 (emphasis added).) The patents' definition of "AAIR" as "using NADPH" contrasts with its definitions for other enzymes, which are limited to enzymes "using NAD[H]" or "utiliz[ing] NADPH ... and/or NADH." (*E.g.*, *id.*, 8:14-16, 8:25-29.)

Moreover, the patents employ the terms "use NADPH" and "NADPH-dependent" synonymously. In discussing an enzyme—"alcohol dehydrogenase VI (ADH6)"—the patents state that it "use[s] NADPH" as a cofactor and equates that use to being "NADPH-dependent":

> [A]lcohol dehydrogenase VI (ADH6) and Ypr1p ... ***use NADPH*** as electron donor. An ***NADPH-dependent*** reductase, YqhD, ... has ***also*** been recently identified in E. coli ....

('188 patent, 12:50-60 (emphasis added).) In addition, the patents also describe ADH6 itself specifically as being an "***NADPH-dependent*** cinnamyl alcohol dehydrogenase" enzyme in Table 1. (*Id.*, 4:60-62, 12:50-60 (emphasis added).)

3. The Patent Office rejected Butamax's attempt to claim all potential enzymes for use in the pathway.

Prosecution history of the '188 patent. The applicants originally sought broad claims, which the Examiner rejected. (A5874, A6922-28.) For each of the five pathway steps, the Examiner found that the claims covered the entire "genus of polypeptides [enzymes] catalyzing" the reaction, not just the specific enzymes described in the specification. (A6294-25.) Accordingly, the Examiner concluded that the claims lacked written description support. (A6925 (application failed to disclose a sufficiently "representative number of species" to capture the entire "genus" of enzymes that could catalyze the five reactions).) The Examiner also found that the disclosure of some specific enzymes "does not reasonably provide enablement for any other embodiment as recited in the claims." (A6926.)

In response, the patentees amended the claims to restrict the claim scope to specific enzymes for each step in the pathway, including the AAIR enzyme for the second step. (A7103.) The patentees conceded that "[c]laim 1 as now amended is limited to an isobutanol producing host cell comprising at least one nucleic acid molecule that ***encodes the enzymes listed in claim 1***." (A7094 (emphasis added).)

After the Examiner again rejected the claims for non-enablement (A7116-19), the patentees reiterated that, in response to the previous office action, the claims had been "amended to recite ***specific enzymes*** as defined by EC number." (A7142 (emphasis added).) Once again, the Examiner rejected the

claims on non-enablement grounds, and the applicants admitted that the amended "claims are commensurate in scope with the teachings in the specification."[12] (A7158; A7147-50.)

In the final Office Action, the Examiner made one anticipation rejection. (A7174-78.) To overcome this rejection, the patentees further amended their claims to require that "each step" of the recited reactions be performed by an enzyme encoded by heterologous DNA. Following this amendment, the Examiner allowed the claims. (A7250-51; A7257-59.)

Prosecution history of the '889 patent. Butamax filed the '889 patent as a divisional from the '188 patent, and the prosecution history proceeded similarly. The patentees originally sought claims with no limitations to specific enzymes. (A7541.) The Examiner rejected the claims on the same written description and non-enablement grounds as in the '188 prosecution history. (A7570-74.)

After an interview, the patentees amended the claims to recite specific enzymes for each recited pathway step. (A7585.) The applicants recognized that, "[a]s amended, the claims provide a method for producing isobutanol ... wherein the pathway comprises substrate to product conversions catalyzed by the ***recited enzymes***." (A7582 (emphasis added).) The applicants further stated: "The ***specific***

[12] At this stage, the patentees also deleted some of the limitations relating to the last step of the pathway, leaving the claim with four steps and a requirement that isobutanol be produced. (A7161.)

enzymes that catalyze the steps of the pathway recited in the claims are described in the application in an abundance of detail." (A7583 (emphasis added).) Following a terminal disclaimer to overcome a double-patenting rejection, the '889 claims were allowed without further comment. (A7593-95; A8512-13.)

4. The allowed claims recite the known pathway steps and known enzymes.

Butamax obtained two independent claims each of which recites the known pathway steps and the known enzymes. Claim 1 of the '188 patent recites:

> 1. A recombinant microbial host cell comprising heterologous DNA molecules encoding polypeptides that catalyze substrate to product conversions for each step below:
>
> i) pyruvate to acetolactate;
>
> ii) acetolactate to 2,3-dihydroxyisovalerate;
>
> iii) 2,3-dihydroxyisovalerate to α-ketoisovalerate; and
>
> iv) α-ketoisovalerate to isobutyraldehyde;
>
> wherein said microbial host cell produces isobutanol;
>
> and wherein
>
> a) the polypeptide that catalyzes a substrate to product conversion of pyruvate to acetolactate is acetolactate synthase having the EC number 2.2.1.6;
>
> ***b) the polypeptide that catalyzes a substrate to product conversion of acetolactate to 2,3-dihydroxyisovalerate is acetohydroxy acid isomeroreductase having the EC number 1.1.1.86***;
>
> c) the polypeptide that catalyzes a substrate to product conversion of 2,3-dihydroxyisovalerate to α-ketoisovalerate is acetohydroxy acid dehydratase having the EC number 4.2.1.9;
>
> d) the polypeptide that catalyzes a substrate to product conversion of α-ketoisovalerate to isobutyraldehyde is

> branched-chain α-keto acid decarboxylase having the EC number 4.1.1.72.

(‘188 patent, claim 1 (emphasis added).)

Claim 1 of the ‘889 patent similarly recites:

> 1. A method for producing isobutanol comprising;
>
> a. providing a fermentation media comprising carbon substrate; and
>
> b. contacting said media with a recombinant yeast microorganism expressing an engineered isobutanol biosynthetic pathway wherein said pathway comprises the following substrate to product conversions;
>
> i. pyruvate to acetolactate (pathway step a);
>
> ii. acetolactate to 2,3-dihydroxyisovalerate (pathway step b);
>
> iii. 2,3-dihydroxyisovalerate to α-ketoisovalerate (pathway step c);
>
> iv. α-ketoisovalerate to isobutyraldehyde (pathway step d); and
>
> v. isobutyraldehyde to isobutanol (pathway step e); and
>
> wherein
>
> a) the substrate to product conversion of step (i) is performed by an acetolactate synthase enzyme;
>
> ***b) the substrate to product conversion of step (ii) is performed by an acetohydroxy acid isomeroreductase enzyme;***
>
> c) the substrate to product conversion of step (iii) is performed by an acetohydroxy acid dehydratase enzyme;
>
> d) the substrate to product conversion of step (iv) is performed by a decarboxylase enzyme; and
>
> e) the substrate to product conversion of step (v) is performed by an alcohol dehydrogenase enzyme; whereby isobutanol is produced.

(‘889 patent, claim 1 (emphasis added).)

* * * * *

In sum, during both the '188 and '889 prosecution histories, the patentees originally sought broad claims not limited to the specific enzymes disclosed and defined in the specification but were forced to limit their claims to those specific enzymes. Accordingly, each recited claim recites an AAIR limitation that necessarily includes its "using NADPH" definition.

C. Gevo Created New NADH-Dependent Enzymes that Balance the Isobutanol Pathway and Are Outside the Scope of Butamax's Claims.

Gevo is a leading renewable chemicals and advanced biofuels company located in Englewood, Colorado. (A3095.) Gevo was founded in 2005 by Drs. Frances Arnold, Matthew Peters, and Peter Meinhold, who worked together at the California Institute of Technology. (*Id.*) Gevo's research has resulted in numerous innovations, including dramatic improvements to the yeast that transform sugar into isobutanol and processing innovations that efficiently separate isobutanol. These innovations enable the low-cost conversion of existing ethanol plants to make isobutanol. Gevo became a public company in 2011 and was the first company to open an industrial scale facility for producing renewable isobutanol.

One of Gevo's key innovations has been the use of directed evolution to develop highly active NADH-dependent KARI enzymes. (A18304-06 at ¶¶ 29-34.) Dr. Arnold and her team analyzed the KARI enzyme and identified target

features. (A18256.) They then mutated those features in thousands of ways. (A18258.) Through careful screening, they found the few enzymes with beneficial mutations, and combined the beneficial mutations from across the new enzymes. (*Id.*) They repeated these steps—focused mutation, careful screening, and combination of beneficial mutations—numerous times until they had created new NADH-dependent KARI enzymes. (A18259.) Gevo's new enzymes and the process by which they were made are described in several references. (A18265-69; A18255-62; *see generally* A10151-91 at ¶¶ 16-91; A18302-08 at ¶¶ 23-33; 57-60.)

Gevo has structurally altered its new KARI enzymes in their active sites, and these structural changes have created profoundly different functional characteristics. (A18306 at ¶ 32.) Unlike the NADPH-dependent AAIR enzymes used by the '188 and '889 patents, Gevo has completely reversed the cofactor dependency of its new KARI enzymes. (A18307-08 at ¶¶ 57-60.) Gevo's engineered enzymes have high efficiency with NADH but have lost 99.9% of their efficiency with NADPH. (A18266-67, Table 49.) The specificity for NADH of Gevo's KARI enzymes (measured in K_m) is more than 26 times greater than its specificity for NADPH. (A10173 at ¶ 49.) This translates into Gevo's new KARI enzymes having a catalytic efficiency for NADH that is 172 times higher than their catalytic efficiency for NADPH. (A10173-75, A10190-91 at ¶¶ 49-52, 89;

A18307-08 at ¶ 59; *see also* A10167, A10190-91 at ¶¶ 68-81, 88-89.) Gevo's new KARI enzymes have balanced the isobutanol pathway, helping increase the yield of isobutanol to more than 90% of the theoretical limit. (*E.g.*, A18261.)

D. Procedural History

1. The district court denied Butamax's motion for a preliminary injunction.

Butamax filed suit in 2011, asserting only the '188 patent. Shortly after the '889 patent issued, Butamax amended its complaint to allege infringement of the '889 patent and moved for a preliminary injunction based on claims 1, 13, and 14 of the '889 patent. The district court granted both parties the opportunity to take extensive discovery. The record considered by the district court for Butamax's preliminary injunction motion included 13 depositions, 10 witness declarations, and hundreds of exhibits. The parties also submitted a full round of briefing prior to a two-day evidentiary hearing, where the district court heard live and video-recorded testimony. Following the hearing, the parties submitted another round of briefing.

In a detailed opinion, the district court denied Butamax's motion, "conclud[ing] that plaintiff does not hold a valid patent, nor would the defendant infringe if it did." (A4494.) The district court construed the term "acetohydroxy acid isomeroreductase" to refer to "an enzyme that is solely NADPH dependent (as opposed to NADH-dependent or NADH and NADPH-dependent)." (A4480.)

Because Gevo's KARI enzymes are NADH-dependent, the district court found that Butamax had not shown a likelihood of success on infringement. (A4482-83.) The district court also held that Gevo had raised a substantial question that several references anticipated the asserted claims and that claim 13 was invalid for lack of written description. (A4487-92.)

2. The Federal Circuit affirmed the preliminary injunction denial.

Following the district court's denial of the preliminary injunction, Butamax appealed to this Court. The panel hearing the appeal affirmed, concluding that Gevo had raised a substantial question as to invalidity. *Butamax™ Advanced Biofuels LLC v. Gevo, Inc.*, 486 F. App'x 883 (Fed. Cir. 2012). The panel, however, expressed concern with the use of the term "solely" in the district court's preliminary injunction construction.[13] *Id.* (A9534:22-A9535:11.) For example, "solely" could be misinterpreted to mean that the claims excluded enzymes that preferred NADPH but had some level of NADH usage, no matter how low.

[13] As Gevo's counsel noted at the hearing, noninfringement does not turn on the word "solely." (A9549:6-22.) The word "solely" was intended only to differentiate between the three recognized categories of enzymes: those that prefer NADPH, those that prefer NADH, and those that have no preference. Contrary to Butamax's attempt to misconstrue Gevo's position, Gevo has never argued that NADPH-dependent enzymes must be 100% specific to NADPH and cannot "use" even low levels of NADH. (A10169-70 at ¶ 44; A17788-89 at ¶¶ 25-27; A17846-47 at ¶¶ 28, 31.)

Accordingly, the panel noted in their opinion that the "trial court should reconsider its construction when it holds a Markman hearing." *Id.*

3. On remand, the district court performed an exhaustive claim construction analysis, and Butamax stipulated to judgment of noninfringement.

The parties continued fact and expert discovery both during the appeal and after the remand. The parties produced over 1.6 million pages of documents, took more than 50 depositions, and submitted 26 expert reports. The parties briefed claim construction again and submitted summary judgment cross-motions on noninfringement and invalidity. The court held an extensive hearing on claim construction and the summary judgment motions.

After conducting a full reconsideration of its preliminary-injunction claim construction, the district court issued its memorandum opinion. (A9-22.) The court began by recognizing that the patents expressly defined "AAIR" as an enzyme "using NADPH." (A9.) The court next examined the patents' definitions, which distinguish enzymes by their use of NADPH and NADH, and the prosecution history, which shows that the patentees amended their claims to recite specific enzymes to overcome repeated rejections. (A11-14.)

The court also carefully considered the extrinsic evidence, performing an exhaustive analysis of the documentary and expert testimony presented by the parties on the meaning and scope of the AAIR term and its express definition. The

court reviewed the entry for the EC number cited by the patent, EC 1.1.1.86, all the references cited in that entry, and all the databases linked to from the EC entry, including the BRENDA database. (A15-20.) Each of those references described AAIR as NADPH-dependent. (*Id.*)

The court then reviewed all the references in the BRENDA database: "In the 43 pages of information contained on the BRENDA database for EC 1.1.1.86, NADH is mentioned in only 16 entries, all of which refer to one or more of only five literature references." (A18.) The court found that four of the five references expressly characterized the studied enzymes as NADPH-dependent. (A18-19.) The district court found that the fifth reference (Rane) described only an enzyme *mutated* to reverse cofactor specificity from being NADPH-dependent to being NADH-dependent. (A19.) Finally, the court analyzed the one additional reference (Xing) cited by Butamax, which was not referenced in the patent, the EC 1.1.1.86 entry, or any of the databases linked to from the EC entry.

After conducting this comprehensive analysis of the intrinsic and extrinsic evidence, the court found that the evidence strongly favored Gevo's proposed construction. (A20-21.) The court reiterated that "the patentees chose to define the KARI enzyme not only by reference to its EC classification, but by its 'use' of NADPH." (A20.) "Having reviewed the scientific literature referenced through the patent's definitional language," the court found that "the patentees' definition

of 'acetohydroxy acid isomeroreductase enzyme' simply reflects the state of the art, that is, that the KARI enzyme known by EC number 1.1.1.86 was generally understood to be NADPH-dependent." (A20-21.)

The court analyzed the two pieces of extrinsic evidence cited by Butamax (Rane and Xing) but found that they did not support Butamax's construction:

> [T]he scientific references almost exclusively characterize KARI enzymes as NADPH-dependent. Of the two references relied on by Butamax to support the use of NADH by KARI enzymes, one (Xing) included a single conclusory sentence with no data or other literature references to support it, and the other (Rane) described having to construct a "quadruple mutant" in order to change a KARI enzyme from being NADPH-dependent to NADH-dependent.

(A20-21.) The court further held that, "even if (or especially if) it was well known in the art that KARI enzymes could 'use' either NADH or NADPH or both, the patentee knew how to describe that and chose not to." (A21 & n.15.) Accordingly, the district court properly concluded that "a person of ordinary skill in the art would understand 'acetohydroxy acid isomeroreductase' to be 'an enzyme known by the EC number 1.1.1.86 that catalyzes the conversion of acetolactate to 2,3-dihydroxyisovalerate and is NADPH-dependent." (A22.)

With this construction, the court ruled on the infringement-related summary judgment motions. Despite recognizing that Butamax's infringement evidence was "less than compelling," the court found disputed fact issues precluding summary judgment of no literal infringement. (A38-39.) The court then held that the

evidence showed, as a matter of law, that the use of NADPH and NADH are not equivalent. (A40-41.)

The district court also granted summary judgment that claims 12 and 13 of the '889 patent are invalid for lack of written description. (A52-55.) Examining each of the passages from the patents Butamax cited as written description support, the district court concluded that the purported description of those claims was nothing more than a legally insufficient wish or research plan. (A51-55.)

During the pretrial conference, conducted the day after the claim construction and summary judgment opinion, Butamax conceded that it could not prove literal infringement. Shortly thereafter, the parties stipulated that the accused Gevo microorganisms do not literally infringe under the district court's construction. (A10758-62.) After severing Gevo's counterclaims into a separate case, the district court issued an amended final judgment, and Butamax filed its notice of appeal. (A144.)

V. SUMMARY OF THE ARGUMENT

Butamax seeks to read out the patents' express definition of the key disputed claim term to cover an enzyme it had not invented. Long before Butamax's patents, the steps of the isobutanol pathway and the enzymes for speeding up the steps were well known. (*See supra* § IV.A.) Persons of skill also knew that natural pathway produces little isobutanol, because the AAIR enzyme in the

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second step strongly prefers to use NADPH as a cofactor, but the chemical reactions preceding the isobutanol pathway produce NADH, not NADPH. This phenomenon is referred to as "cofactor imbalance."

At the time it filed the patents-in-suit, Butamax recognized that the AAIR enzyme's use of NADPH created a cofactor imbalance. (*See infra* § VII.A.3.)

Rather than waiting to seek a patent until it had solved this problem, Butamax filed an application based on its use of the known enzymes in the known isobutanol pathway. (*See infra* § VII.A.1.) Due to the limited scope of its purported invention, Butamax expressly defined "AAIR" as "an enzyme that catalyzes the conversion of [AL] to [DHIV] ***using NADPH*** ... as an electron donor." ('188 patent, 7:35-40 (emphasis added).)

Notwithstanding its purported *NADPH-dependent* invention, Butamax has attempted in this litigation to expand the claim scope to cover Gevo's bioengineered *NADH-dependent* enzymes. Butamax continues these efforts on

appeal with both primary and back-up claim construction positions. Both positions conflict with the patents' express definition.

Butamax's primary position ignores the "using NADPH" requirement entirely, attempting to interpret "AAIR" as encompassing any "enzyme that catalyzes the conversion of AL to DHIV," irrespective of cofactor. (BM Br. at 34.)

Butamax's primary claim construction contradicts the intrinsic record. (*See infra* § VII.A.1.) For each patent, Butamax attempted to obtain claims that would have covered both the known enzymes Butamax described in the specification and enzymes Butamax had not invented. The Examiner refused, rejecting the claims under 35 U.S.C. § 112. In response, Butamax amended the claims by limiting them to the "specific enzymes" described in the patents, including a limitation to the AAIR enzyme and its defined use of NADPH. (A7142; A7583.)

Butamax's back-up claim construction similarly seeks to negate the patents' "using NADPH" definition, asserting that an enzyme with any detectable activity with NADPH in a test tube comes within the claim scope.

Butamax's back-up construction also contradicts the intrinsic record. (*See infra* § VII.A.2.) The patents employ the phrase "using NADPH" consistently with its customary meaning in this field, expressly equating the phrase "use[s] NADPH" with being "NADPH-dependent." (*Compare* '188 patent, 12:50-60, *with id.*, 4:60-62 (describing ADH6 enzyme).) Moreover, the patents carefully distinguish

several enzymes based on their cofactor preferences. They define the AAIR enzyme as "using NADPH," a different enzyme as "using NAD[H]," and another enzyme as "utilizing NADPH … and/or NADH." Butamax's back-up construction renders those carefully constructed distinctions meaningless, because its detectability threshold is so low that all the relevant defined enzymes would "use" both NADPH and NADH under its construction.

Having no support in the intrinsic record, Butamax focuses on extrinsic evidence—the Arfin, Rane, and Xing references the district court considered within its exhaustive analysis of the entire scientific record. (*See infra* § VII.A.2.c, VII.A.4.) The district court analyzed the Enzyme Commission ("EC") entry recited in the patent, all references cited in the EC entry, all databases linked to from the EC entry, all references cited within those databases, and all other references cited by Butamax. After this detailed review, the district court correctly found that "the patentees' definition of 'acetohydroxy acid isomeroreductase enzyme' simply reflects the state of the art, that is, that the KARI enzyme known by EC number 1.1.1.86 was generally understood to be NADPH-dependent." (A19-20.)

Under the district court's construction that the claimed AAIR enzyme is NADPH dependent, Butamax conceded that it could not prove literal infringement. The district court also correctly granted summary judgment of no infringement

under the doctrine of equivalents. As detailed below, the district court's decision is well-supported by the record and may also be affirmed under the doctrine of prosecution history estoppel. (*See infra* § VII.B.2.)

Butamax's appeal also addresses the district court's grant of summary judgment of invalidity of claims 12 and 13 of the '889 patent for lack of written description. (*See infra* § VII.C.) These claims recite the inactivation of genes that express enzymes that could divert away resources from the isobutanol pathway, because they use the same ingredients as the isobutanol pathway but produce different chemicals. As the district court held, the specification contains no suggestion that the named inventors actually possessed these claimed invention as of the filing date. Accordingly, the district court properly granted summary judgment of invalidity.

VI. STANDARD OF REVIEW

The judgment of no literal infringement turns on claim construction, because Butamax stipulated to no literal infringement under the district court's construction. Under *Cybor*, claim construction is reviewed by this Court de novo. *Cybor Corp. v. FAS Techs., Inc.*, 138 F.3d 1448 (Fed. Cir. 1998) (en banc). The *Cybor* rule, however, is currently being reheard en banc in *Lighting Ballast Control LLC v. Philips Elecs. N. Am. Corp.*, 500 F. App'x 951 (Fed. Cir. 2013).

To the extent that *Lighting Ballast* modifies *Cybor*, the district court's decision in this case should be afforded substantial deference. The district court issued a well-reasoned, detailed claim construction decision that carefully analyzed both the intrinsic evidence and extrinsic scientific evidence regarding the historical, art-specific meanings of the patent terms. The district court also made its decision on a full record. It heard testimony during the preliminary injunction proceedings, reviewed many rounds of briefing, and held oral argument. Moreover, the district court decided claim construction at the end of the case, having the benefit of fully developed fact and expert discovery.

The judgments of noninfringement under the doctrine of equivalents and invalidity for lack of written description both resulted from a grant of summary judgment. This Court "review[s] a district court's grant of summary judgment *de novo*, reapplying the same standard applied by the district court." *Duramed Pharms., Inc. v. Paddock Labs., Inc.*, 644 F.3d 1376, 1379-80 (Fed. Cir. 2011) (affirming summary judgment of noninfringement under the doctrine of equivalents); *Atl. Research Mktg. Sys., Inc. v. Troy*, 659 F.3d 1345, 1353-56 (Fed. Cir. 2011) (same re written description).

VII. ARGUMENT

A. The District Court Correctly Construed the AAIR Limitation.

1. Butamax's primary proposed claim construction would read out the patents' express definition, which limits the "AAIR" term to enzymes "using NADPH."

Each asserted independent claim requires the use of an AAIR enzyme. ('188 patent, claim 1; '889 patent, claim 1.) Butamax's principal claim construction position is that AAIR's "plain meaning" encompasses any "enzyme that catalyzes the conversion of AL to DHIV." (BM Br. at 34.) Butamax's argument contradicts the patent specifications and the prosecution history.

The patents include materially identical definitions sections, which state unmistakably that "[t]he following definitions and abbreviations ***are to be used*** for the interpretation of the claims and specification." ('188 patent, 7:12-14 (emphasis added).). *AstraZeneca AB v. Mut. Pharms. Co., Inc.*, 384 F.3d 1333, 1339-40 (Fed. Cir. 2004) (definitions section "provides a strong signal of lexicography"). The patents expressly define "AAIR":

> The terms "acetohydroxy acid isomeroreductase" and "acetohydroxy acid reductoisomerase" ***are used interchangeably herein to refer to an enzyme*** that catalyzes the conversion of acetolactate to 2,3-dihydroxyisovalerate ***using NADPH*** (reduced nicotinamide adenine dinucleotide phosphate) as an electron donor.

('188 patent, 7:35-40 (emphasis added).)

As the district court correctly held, persons of skill would understand the patents as using lexicography defining the scope of the AAIR enzyme. (A19 ("[T]he patentees chose to define the KARI enzyme ... by its 'use' of NADPH."); A17818-19 at ¶¶ 45-50; A17786 at ¶¶ 19-21; A17845 at ¶¶ 25-27.) The patents define the term in a separate definitions section, offset the term in quotation, and use the word "herein" to make clear that the express definition applies throughout the patents. Those are the hallmarks of express lexicography. *Sinorgchem Co. v. ITC*, 511 F.3d 1132, 1136 (Fed. Cir. 2007) (quotation marks and "is" indicate lexicography). Accordingly, the "inventor[s'] lexicography governs." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1316 (Fed. Cir. 2005) (en banc); *Renishaw PLC v. Marposs Societa' per Azioni*, 158 F.3d 1243, 1249 (Fed. Cir. 1998).

Giving meaning to the patents' definition of AAIR is especially critical here, because Butamax received the '188 and '889 patents only after amending the claims to limit their scope to specific enzymes. The Patent Office rejected Butamax's proposed claims on 112 grounds, because they attempted to claim the broad "genus" of all enzymes for performing the recited reactions of the isobutanol pathway. (A6922-28; A7570-74.) In response, Butamax amended the claims to add the enzyme limitations, arguing that the Patent Office should allow the claims because they were limited to only the "***specific enzymes***" described in the patents. (A7142 (emphasis added); A7583 (emphasis added).) Butamax's so-called "plain

meaning" construction—which would broaden the claims to cover any "enzyme that catalyzes the conversion of AL to DHIV" (BM Br. at 34)—improperly tries to recapture the claim scope it willingly conceded during prosecution.

2. Butamax's back-up construction conflicts with the intrinsic record.

In addition to its primary construction, which seeks to read out the "using NADPH" definition entirely, Butamax also offers a secondary, back-up claim construction. Butamax's back-up construction interprets the phrase "using NADPH" as requiring only that the accused AAIR enzyme have a minimal detectable level of NADPH activity. As detailed below, both the intrinsic and extrinsic evidence strongly support the district court's construction of "using NADPH" as referring to the *relative* usage of NADPH over NADH—*i.e.*, its "preference" for or "dependence" on NADPH—not any *absolute*, detectable level of NADPH activity.

a. The patents employ "using NADPH" and "NADPH-dependent" interchangeably.

The patents employ the terms "use NADPH" and "NADPH-dependent" interchangeably. For example, in discussing the enzyme "alcohol dehydrogenase VI (ADH6)," the patents state that it "use[s] NADPH" as a cofactor and equates that use to being "NADPH-dependent":

> [A]lcohol dehydrogenase VI (ADH6) and Ypr1p ... ***use NADPH*** as electron donor. An ***NADPH-dependent*** reductase, YqhD, ... has ***also*** been recently identified in E. coli ....

('188 patent, 12:50-60 (emphasis added).) In addition to describing ADH6 as "us[ing] NADPH" in the detailed description, the patents also describe ADH6 itself specifically as being an "***NADPH-dependent*** cinnamyl alcohol dehydrogenase" enzyme in Table 1. (*Id.*, 4:60-62, 12:50-60 (emphasis added).) This description of ADH6 is consistent with the recognition by persons of skill that ADH6 is "NADPH-dependent." (A18291 ("NADPH-dependent medium chain alcohol dehydrogenase with broad substrate specificity").)

Thus, contrary to Butamax's proposed construction, the '188 and '889 patents themselves recognize that persons of skill in this field employ the phrase "use NADPH" to mean being "NADPH-dependent."

b. Butamax's back-up construction contradicts the patents' express definitions.

Butamax's back-up construction would also render the patents' careful definitions meaningless. (A14-15, A21.) The patents' express definitions categorize enzymes into three groups based on co-factor usage: "using NADPH," "using NAD+" (the oxidized form of NADH), and "using either NADH and/or NADPH." For example:

- AAIR is "an enzyme that catalyzes the conversion of acetolactate to 2,3-dihydroxyisovalerate ***using NADPH*** ... as an electron donor." ('188 patent, 7:35-40 (emphasis added).)

- "[B]ranched-chain keto acid dehydrogenase" is "an enzyme that catalyzes the conversion of α-ketoisovalerate to isobutyryl-CoA (isobutyryl-coenzyme A), ***using NAD+*** ... as electron acceptor." (*Id.*, 8:25-29 (emphasis added).)

- "[B]ranched-chain alcohol dehydrogenase" is "an enzyme that catalyzes the conversion of isobutyraldehyde to isobutanol ... ***utiliz[ing] NADH ... and/or NADPH*** as electron donor." (*Id.*, 8:14-16 (emphasis added).)

These distinctions collapse if Butamax's construction is adopted, because both Gevo and Butamax agree that all known nicotinamide-related enzymes[14] have some activity level for both NADPH and NADH. (*Compare* A10166 at ¶ 37, *with* A18324; A18326 & A18328-29, 149:16-21, 169:11-170:11.[15]) Thus, under Butamax's construction, AAIR, keto acid dehydrogenase, and alcohol dehydrogenase would all "use" both NADPH and NADH. But the patentees chose to distinguish between the enzymes, describing AAIR as "using NADPH," keto acid dehydrogenase as "using NAD+," and alcohol dehydrogenase as using both.

Distinguishing enzymes based on "using" NADPH, NADH, or both, is fully consistent with how persons of skill use those phrases. (A10156-63 at ¶¶ 25-34.) For example, the EC entry for an NADH/NADPH enzyme refers to the enzyme as "NAD(P)+-dependent," which means that the enzyme "can use NAD+ and NADP+ with similar specific activity." (A10160 at ¶ 29 (citing E.C. 1.1.1.299).)

[14] This brief uses the term "nicotinamide-related enzymes" to refer to enzymes that employ NADPH, NADH, or both as a cofactor.

[15] As a specific example, Gevo tested an NADPH-dependent wild-type KARI and found detectable, though minimal, activity with NADH. (A18266-67, Table 49.)

The same entry also notes that this enzyme is "different from" corresponding enzymes that prefer NAD+ or NADP+, confirming the longstanding practice in the art of distinguishing enzymes based on which cofactor they prefer. (*Id.*)

Accordingly, where the patents wanted to define an enzyme as being able to use either NADPH or NADH, they did so. Because the patentees expressly chose to define AAIR as "using NADPH"—and not "using NADPH and/or NADH"—that decision limits the scope of the claims. *Abbott Labs. v. Sandoz, Inc.*, 566 F.3d 1282, 1290, 1296-97 (Fed. Cir. 2009) (construing the term "crystalline" to mean "Crystal A" because the patentee's use of "Crystal B" in a related application demonstrated its intent to limit the patent); *Kao Corp. v. Unilever U.S., Inc.*, 441 F.3d 963, 973 n.5 (Fed. Cir. 2006) ("If Kao had intended to claim salt forms of the copolymer in the '382 Patent, the subsequent patent application would have been superfluous.").

c. The Arfin reference is extrinsic evidence and does not define "AAIR."

Butamax's focus on the Arfin reference also conflicts with the patents. Contrary to Butamax's claim that Arfin is the "gold standard" and a "seminal reference" (BM Br. at 41, 43), the patents' definition does not mention the Arfin reference at all. A search through the patents as a whole results in only one hit on "Arfin," in describing a measurement of the activity of the AAIR in a prophetic example. ('188 patent, 33:45-48.) Other than that one reference to the publication

in the specification, "Arfin" is not mentioned at all during the prosecution history. Accordingly, nothing in the intrinsic record suggests that the particular methodology referenced in Arfin has any bearing on the definition of AAIR provided by the patents.

Arfin itself is extrinsic evidence, because it was never incorporated by reference or otherwise made a part of the intrinsic record. Even if the Arfin reference were part of the intrinsic record, its artificial test-tube environment does not measure the AAIR enzyme's behavior in a microorganism. The asserted claims all require that the pathway steps occur in a "microbial host cell" or a "recombinant yeast microorganism." ('188 patent, claim 1; '889 patent, claim 1.) Arfin's methodology, however, relates only to "cell-free extracts" and artificially purified enzymes, not live cells. (A10143; A18371-72.)

This conflict between the *in vivo* nature of the claims and the *in vitro* nature of Butamax's proposed back-up construction further demonstrates its inappropriateness. As Gevo's expert witnesses stated, "it is possible to force nearly any NADPH-dependent enzyme to use NADH by creating sufficiently artificial conditions for the reaction" and vice-versa. (A18302 at ¶ 25.) Butamax's experts agreed: "Where the only cofactor in the environment is NADPH, such as in the Arfin ... assay, a KARI will use that cofactor exclusively ***because it is the only***

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one present.... In environments like living yeast cells, both cofactors are present in varying concentrations." (A4594 (Rabinowitz) ¶ 36 (emphasis added).)

Accordingly, the district court properly declined to incorporate the Arfin methodology into the definition of "AAIR."

3. Butamax's internal, pre-suit documents confirm that "using NADPH" means "NADPH-dependent."

a. Butamax launched a research program to create an "NADH-dependent" AAIR enzyme.

[redacted]

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[redacted]

These pre-suit communications provide strong admissions that the ordinary and customary meaning of "using NADPH" in this field refers to NADPH preference and dependence, not detectability.

b. The result of Butamax's research program—the Li application—equates "uses NADH" with NADPH-dependence.

In December 2008, Butamax filed a new patent application (the "Li application") that described Butamax's first alleged discovery of an NADH-dependent AAIR enzyme. (A8778.) The Li application was titled "Ketol-acid reductoisomerase ***using*** NADH." (*Id.* (emphasis added).) The Li application concedes that Butamax knew of no prior NADH-dependent KARI enzymes:

[redacted]

> ***[T]o date the only ketol-acid reductoisomerase (KARI) enzymes known are those that bind NADPH in its native form, reducing the energy efficiency of the pathway.*** A KARI that would bind NADH would be beneficial and enhance the productivity of the isobutanol biosynthetic pathway by capitalizing on the NADH produced by the existing glycolytic and other metabolic pathways in most commonly used microbial cells. ***The discovery of a KARI enzyme that can use NADH as a cofactor as opposed to NADPH would be an advance in the art.***

(A8794, ¶¶ 6, 9 (emphasis added).)

The Li application also employs the term "use" to mean "preference":

> [K]etol-acid reductoisomerase enzymes have been evolved to ***use the cofactor NADH instead of NADPH***.
>
> ....
>
> Applicants have solved the stated problem by identifying a number of mutant ketol-acid reductoisomerase enzymes that ***have a preference for binding NADH as opposed to NADPH***.

(A8794, ¶¶ 2, 10 (emphasis added); A8800, ¶¶ 81-82 (describing KARI enzymes "evolved to ***utilize NADH*** as a cofactor" and as being "***specific for NADH***") (emphasis added).) The Li application likewise uses the phrases "NADPH-dependent" in referring to several enzymes. (*See* A8794, A8803, ¶ 7 ("strictly NADPH-dependent p-Hydroxybenzoate hydroxylase (PHBH)"); *id.*, ¶ 134 ("NADPH-dependent reductase, YqhD").)

c. Butamax amended the definition of "AAIR" to include NADH-dependent AAIR enzymes only after the Li application.

After the Li application, Butamax filed a continuation-in-part application (the "Donaldson application") that claimed priority to both the '188 patent and the Li application. (A8897.) The Donaldson application amended the definition of AAIR to state that it "use[s] electron donors such as NADPH **and/or NADH** for the conversion of acetolactate to 2,3-dihydroxyisovalerate." (A8903, ¶ 55 (newly added language emphasized).) Accordingly, Butamax expressly expanded the definition of "AAIR" to include NADH-dependent enzymes and did so only after the Li application finally described them.

* * * * *

In sum, Butamax's own pre-suit documentation supports Gevo's construction, because it employs "using," "preferring," and "dependent" synonymously and shows Butamax's own recognition that the purported inventions in the '188 and '889 patents did not include an NADH-dependent AAIR enzyme.

4. The district court's careful inspection of the entire record provides strong support for its construction.

After carefully examining the intrinsic record, the district court extensively investigated the scientific record provided by the parties. As detailed below, the district court's findings regarding the state of the art present the type of well-reasoned, detailed factual analysis entitled to as much deference as the law affords.

a. The entry for Enzyme Commission number 1.1.1.86 supports the court's construction.

(1) The EC rules require distinguishing natural enzymes into three groups: using NADPH, using NADH, or using either NADPH or NADH.

The patents state that "[p]referred acetohydroxy acid isomeroreductases are known by the EC number 1.1.1.86." ('188 patent, 7:40-43.) As the district court recognized, the Enzyme Commission ("EC") numbering system classifies naturally occurring enzymes by the reactions they catalyze. (A10155-56 at ¶¶ 22-24; A17781 at ¶ 10; A17837 at ¶ 11.)

For enzymes that use nicotinamide cofactors, the EC Rules require specifying the cofactor and providing separate EC numbers for naturally occurring enzymes with different cofactor preferences: "For oxidoreductases using NAD+ or NADP+, the coenzyme should always be named [as the acceptor] .... Where the enzyme can use either coenzyme, this should be indicated by writing NAD(P)+." (A7068; A10156 at ¶¶ 25-26; A17781-82, A17787, A17789-90 at ¶¶ 11-13, 22, 28; A17837-39, A17847-49 at ¶¶ 12-16, 33-34, 37.) The EC system includes many examples of enzymes that have different EC numbers because they prefer different nicotinamide cofactors. (A10156-63 at ¶¶ 25-34; A17839-41 at ¶¶ 17-18; A17782 at ¶¶ 12-13.) These three EC categories track the same three categories from the

patents. (A17842 at ¶¶ 19-20; A17782-83 at ¶ 14; A17809-10, A17813-15 at ¶¶ 29-31, 38-39.)

(2) The EC 1.1.1.86 entry characterizes AAIR enzymes as NADPH-dependent.

As the district court correctly found, the entry for EC 1.1.1.86 describes AAIR as an NADPH-dependent enzyme. (A15-16; *see generally* A17837-50 at ¶¶ 11-39; A17781-90 at ¶¶ 10-29.) The relevant portion of the EC entry is highlighted below:

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IUBMB Enzyme Nomenclature

EC 1.1.1.86

Accepted name: ketol-acid reductoisomerase

Reaction: (*R*)-2,3-dihydroxy-3-methylbutanoate + $NADP^+$ = (*S*)-2-hydroxy-2-methyl-3-oxobutanoate + NADPH + H^+

For diagram of reaction click here.

Other name(s): dihydroxyisovalerate dehydrogenase (isomerizing); acetohydroxy acid isomeroreductase; ketol acid reductoisomerase; a-keto-ß-hydroxylacyl reductoisomerase; 2-hydroxy-3-keto acid reductoisomerase; acetohydroxy acid reductoisomerase; acetolactate reductoisomerase; dihydroxyisovalerate (isomerizing) dehydrogenase; isomeroreductase; reductoisomerase

Systematic name: (*R*)-2,3-dihydroxy-3-methylbutanoate:$NADP^+$ oxidoreductase (isomerizing)

Comments: Also catalyses the reduction of 2-aceto-2-hydroxybutanoate to 2,3-dihydroxy-3-methylpentanoate.

Links to other databases: BRENDA, EXPASY, KEGG, PDB, CAS registry number: 9075-02-9

References:

1. Arfin, S.M. and Umbarger, H.E. Purification and properties of the acetohydroxy acid isomeroreductase of *Salmonella typhimurium*. *J. Biol. Chem.* 244 (1969) 1118-1127. [PMID: 4388025]

2. Hill, R.K., Sawada, S. and Arfin, S.M. Stereochemistry of valine and isoleucine biosynthesis. IV. Synthesis, configuration, and enzymatic specificity of a-acetolactate and a-aceto-a-hydroxybutyrate. *Bioorg. Chem.* 8 (1979) 175-189.

3. Kiritani, K., Narise, S. and Wagner, R.P. The reductoisomerase of *Neurospora crassa*. *J. Biol. Chem.* 241 (1966) 2047-2051.

4. Satyanarayana, T. and Radhakrishnan, A.N. Biosynthesis of valine and isoleucine in plants. 3. Reductoisomerase of *Phaseolus radiatus*. *Biochim. Biophys. Acta* 110 (1965) 380-388. [PMID: 5866387]

[EC 1.1.1.86 created 1972, modified 1976, modified 1981 (EC 1.1.1.89 created 1972, incorporated 1976)]

(A4778 at 1 (highlighting added); A17813-15, A17816-17, A17819-20 at ¶¶ 38-39, 43-44, 52; A17783-86, A17789-90 at ¶¶ 16-18, 28; A17843 at ¶¶ 22-24.)

Butamax raises two arguments against the district court's findings. Butamax first argues that the 2005 version of EC 1.1.1.86 was intended to encompass all three categories of nicotinamide dependence. (BM Br. at 45.) Butamax's argument contradicts the EC Rules, which require different numbers based on

nicotinamide preference. (A17789-90 at ¶¶ 28-29; A17838, A17847-49 at ¶¶ 14, 33-34, 37.) Butamax's argument also ignores the fact that no additional category needed to be created, because no known natural NADH-dependent AAIR enzymes existed. (A17815-16 at ¶¶ 40-42.)

Butamax next contends that the intermittent use by Gevo scientists of the 1.1.1.86 number in referring to their new KARI shows that the EC number is not limited to NADPH-dependent enzymes. (BM Br. at 25.) Butamax's argument fails because the EC classification system does not assign new numbers to bioengineered enzymes, as Butamax's expert conceded. (A4654 (Schomburg) ¶ 69; *see also* A17842-43 at ¶ 21; A17810-11 at ¶ 15; A17810-11 at ¶¶ 32-33.) Because no assignments are made for bioengineered enzymes and no naturally occurring NADH-dependent KARI enzymes have been recognized, Gevo scientists have sometimes used the 1.1.1.86 number as the closest reference. (A4366-67, A4450, A4452-53, 188:23-190:21, 381:18-21, 389:24-390:4.)

Accordingly, the patents' reference to the EC entry 1.1.1.86 further supports the district court's construction.

b. The publications related to the EC 1.1.1.86 entry further demonstrate that AAIR was known to be NADPH-dependent.

The district court next scrutinized all the information related to the EC 1.1.1.86 entry. The district court examined the four references cited in the EC

1.1.1.86 entry, correctly finding that each described the catalyzed reaction as using NADPH. (A16-17.) The court then examined each database cited in the 1.1.1.86 EC entry. (A18.) As the district court found, each of the entries in the databases linked to from the EC 1.1.1.86 entry likewise describes naturally occurring AAIR enzymes as NADPH-dependent. (A18.)

One of these databases—BRENDA—also included specific literature citations, so the court inspected those as well. The district court located only five references that discussed NADH on 43 pages of citations in BRENDA. (A18.) The court found that four of the five references expressly characterized the studied enzymes as NADPH-dependent. (A18-19.) The district court also considered the fifth BRENDA reference (Rane), which described an enzyme *mutated* to reverse cofactor specificity and the Xing reference cited by Butamax, which was not cited in the patent, the EC 1.1.1.86 entry, or any of the databases linked to from the EC entry.

After examining all the intrinsic and extrinsic evidence in detail, the court concluded that the overwhelming weight of the evidence required construing "using NADPH" to mean "NADPH-dependent." (A20-21.) The court started with the premise that "patentees who choose to provide definitions should be especially mindful of being their own lexicographers." (A20-21 (concluding that "the patentees' definition of 'acetohydroxy acid isomeroreductase enzyme' simply

reflects the state of the art, that is, that the KARI enzyme known by EC number 1.1.1.86 was generally understood to be NADPH-dependent").) From the extensive documentary and expert evidence, the district court made additional findings regarding the art-specific meaning of "using NADPH":

- NADPH and NADH serve distinct metabolic functions, despite having similar chemical structures;
- enzymes using NADPH are "frequently termed ... NADPH-dependent";
- "all natural AAIR enzymes were known to be NADPH-dependent" in 2005; and
- "[a]lthough 'the limits of biology virtually guarantee that all KARI enzymes will have at least some ancillary activity with both cofactors,' a person of ordinary skill in the art would understand that an enzyme that 'uses NADPH' or that 'uses NADH' is 'NADPH-dependent' or 'NADH-dependent,' respectively."

(A15-16, A20.)

On appeal, Butamax focuses on only two of the vast number of references and pieces of evidence the district court considered in reaching its claim construction. The district court specifically considered those two references (Rane and Xing), but concluded that they did not justify Butamax's proposed expansive construction of the patents. (A20-21.) The court also found that these references contradicted the patents' express definition of AAIR. (A21 & n.15 (noting that the patentees knew how to describe NADH-dependent enzymes, but "chose not to").)

The district court's findings regarding Rane and Xing are well-supported in the record. Contrary to Butamax's argument, the Rane and Xing references are not "preferred embodiments" excluded by the district court's construction. The Rane reference has only the most distant connection to the patents: the patents' AAIR definition mentions EC 1.1.1.86, which includes a link to four external databases, one of which includes a long 46-page list of journal articles, of which just one references purports to have mutated a KARI enzyme so that it prefers NADH. The Xing reference has no connection to the patents at all.

Moreover, neither Rane nor Xing has any connection to the four specific enzymes listed in the patent as preferred embodiments. "Of these four enzymes, the first two have been previously characterized and found to be NADPH-specific" and the "cofactor-specificity of the other two enzymes has not been studied." (A17846 at ¶ 29.) For example, the basis for the *Methanococcus maripaludis* sequence listed in the patent is the Hendrickson article. (A18270 (referencing Hendrickson); A18271 (same).) The Hendrickson article shows that the relevant AAIR enzyme uses NADPH. (A18288.)

Accordingly, the vast weight of the scientific evidence cited by the parties, particularly the evidence cited in the patents, supports the district court's findings that the ordinary and customary meaning of the patents' definition of AAIR as "using NADPH" refers to "NADPH-dependence."

5. Butamax's claim differentiation arguments fail.

Butamax also argues that claim differentiation supports its proposed construction, pointing to only two claims.

Claim 15 of the '188 patent. Butamax argues that dependent claim 15 of the '188 patent shows an NADH-dependent or "dual dependent" *Methanococcus* enzyme and, therefore, implies that claim 1 must also cover NADH-dependent AAIR enzymes. (BM Br. at 39-40.) This argument tracks the same evidence addressed immediately above for the Xing reference. The district court properly rejected Butamax's attempt to expand the scope of its claims based on an uncited, unverified source purporting to show that an enzyme in the *Methanococcus* genus had some NADH activity. (A19-20.)

Claim 14 of the '889 patent. Claim 14 does not meet the limited circumstances in which claim differentiation can apply—where a narrow construction of the independent claim would render the dependent claim wholly superfluous. *Enzo Biochem, Inc. v. Applera Corp.*, 599 F.3d 1325, 1342 (Fed. Cir. 2010) (an independent claim broader than the dependent claim in any way "simply does not implicate the doctrine of claim differentiation").

Claim 14 depends directly from claim 1, which recites five enzymes. The last recited enzyme—alcohol dehydrogenase—is defined as including specific enzymes that use *either* NADPH *or* NADH. ('889 patent, claim 1, 7:49-58.) By

requiring that at least one recited enzyme to use NADH, claim 14 narrows the scope of the alcohol dehydrogenase term. Because the district court's construction thus does not render claim 14 superfluous, claim differentiation does not apply. *Enzo Biochem*, 599 F.3d at 1342.

Ignoring that fact, Butamax argues that the words "or more" in claim 14 means that the claimed AAIR enzyme must also be capable of using NADH. (BM Br. at 38.) The district court correctly rejected Butamax's argument.[17] Butamax's construction would create a direct conflict between claims 1 and 14, requiring "AAIR" to be defined as "using NADPH" for claim 1 and as "using NADH" for dependent claim 14.[18] Butamax's construction also fails, because it would sweep within the claim scope the NADH-dependent enzyme Butamax had not invented by 2005.[19] Because claim 14 was added by Butamax long after the patents' priority date and after the Li application was filed, it provides no contemporaneous

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[17] *Eon-Net LP v. Flagstar Bancorp.*, 653 F.3d 1314, 1323 (Fed. Cir. 2011) ("[C]laim differentiation is a rule of thumb that does not trump the clear import of the specification.") (internal quotation omitted); *Power Mosfet Techs., LLC v. Siemens AG*, 378 F.3d 1396, 1409-10 (Fed. Cir. 2004) (claim differentiation canon "is not inflexible.") (internal quotation omitted).

[18] *Regents of the Univ. of Cal. v. Dakocytomation Cal., Inc.*, 517 F.3d 1364, 1375 (Fed. Cir. 2008) (claim differentiation must yield where "a contrary construction [is] dictated by the written description").

[19] *Tandon Corp. v. U.S. Int'l Trade Comm'n*, 831 F.2d 1017, 1024 (Fed. Cir. 1987) ("Whether or not claims differ from each other, one can not interpret a claim to be broader than what is contained in the specification and claims as filed."); *Curtiss-Wright Flow Control Corp. v. Velan, Inc.*, 438 F.3d 1374, 1380-81 (Fed. Cir. 2006).

evidence justifying an inference broadening the scope of the patents-in-suit. (A7542 ('889 claim 14 added on November 3, 2010); A8778 (Li application filed December 18, 2008).)

Finally, adopting Butamax's proposed construction would create the very problem it purports to be solving. Because Butamax's expansive definition would mean that all nicotinamide-related enzymes "use" both NADPH and NADH, claim 14's addition of "uses NADH" language would not narrow the claim scope in any way.[20]

6. Butamax's indefiniteness argument is mistaken and disingenuous.

As it argued during the prior appeal, Butamax contends again that the term "NADPH dependent" is so vague that it would render the asserted claims indefinite. (BM Br. at 52-55.) During the prior appellate argument, Butamax's counsel asserted: "[T]here's nothing in the specification or the prosecution history that says NADPH-dependent." (A9535-36; A9540 ("But enzymes don't prefer.").) These statements are simply not true.

Butamax's attorney argument conflicts with its own patents, its internal documents, and its actions in this case. The '188 and '889 patents expressly use the phrase "NADPH-dependent" and do so interchangeably with "use NADPH." (*See supra* § VII.A.2.a.) Numerous Butamax documents, including internal

[20] *ICU Med., Inc. v. Alaris Med. Sys., Inc.*, 558 F.3d 1368, 1376 (Fed. Cir. 2009).

documents and its patents and applications, also repeatedly employ the phrases "dependent," "prefers," and "selective" in referring to enzymes that use NADPH. (*See supra* § VII.A.3.)

After the district court denied Gevo's motion for summary judgment, Butamax's counsel explained her understanding of the "three buckets" grouping of enzymes that use the nicotinamide cofactors and concluded that Butamax could not prove infringement under the court's construction. (A10831, 11:6-20.) Butamax stipulated to noninfringement, effectively conceding that the district court's "NADPH dependent" claim construction was sufficiently definite to resolve the noninfringement dispute presented by the parties. This concession bars its indefiniteness argument on appeal. Butamax's experts also confirmed that, in a tripartite system that distinguishes between enzymes that prefer NADPH, those that prefer NADH, and those that do not have a preference for either, Gevo's KARI enzyme does not depend on NADPH. (A18336 & A18338, 120:13-25, 121:10-122:4, 132:5-133:17.)

Accordingly, Butamax's argument that the phrase "NADPH-dependent" is vague and indefinite directly contradicts the record of its own admissions outside of litigation.

7. The Court should reject Butamax's remaining arguments.

In addition to its Arfin, Rane, and Xing arguments, Butamax's brief provides a shotgun list of additional arguments attempting to support its construction.

First, Butamax contends that its broader proposed claim construction must be adopted unless Gevo shows a "disavowal of claim scope" or "manifest exclusion or restriction." (BM Br. at 46, 50.) Butamax misconstrues Federal Circuit law. As *Phillips* made clear, claims must be interpreted "with a full understanding of what the inventors actually invented." *Phillips*, 415 F.3d at 1316 (internal quotation omitted).[21] Where a claim term has a clear and unmistakable ordinary meaning to persons of skill in the art, courts reasonably require a clear and unmistakable disclaimer to overcome that meaning. Where a claim term may reasonably be interpreted in several ways, no canon of construction imposes a heavy one-sided burden favoring broad constructions over narrow ones or favoring patent-owners over accused infringers. Instead, courts weigh all of the evidence and provide the construction that most "naturally aligns" with the scope of the actual invention. *Id.*

Second, Butamax argues that the district court's construction should be rejected because it imposes a "negative" limitation, citing *Martek Biosciences*

[21] *Retractable Techs., Inc. v. Becton, Dickinson & Co.*, 653 F.3d 1296, 1305 (Fed. Cir. 2011), *cert. denied*, 133 S.Ct. 833 (2013) ("In reviewing the intrinsic record to construe the claims, we strive to capture the scope of the actual invention ....").

Corp. v. Nutrinova, Inc., 579 F.3d 1363 (Fed. Cir. 2009). The *Martek* case does not support Butamax's argument; it says nothing about "negative" or "positive" limitations. Nor does that distinction make sense. The district court's construction here works like every other claim construction to set a boundary between what is included within the claim scope (the "positive" aspect of the construction) and what is excluded from the claim scope (the "negative" aspect of the construction).

Third, Butamax argues that "[i]t would be illogical ... to exclude KARIs that are 'NADH-dependent' ... because such KARIs are useful in the claimed engineered pathway." (BM Br. at 36-37.) NADH-dependent KARI enzymes certainly are useful, but there is nothing "illogical" about limiting the claim scope to what Butamax purported to actually invent.

Fourth, Butamax contends that the strong preference of Gevo's NADH-dependent KARI enzyme for NADH is merely an "additional feature" that does not preclude infringement. (BM Br. at 46.) To the contrary, as a result of Butamax's lexicography and prosecution history, cofactor-dependence is itself a part of the definition of the AAIR element itself. In addition, Gevo's successful reversal of the KARI enzyme's cofactor dependence fundamentally alters the reaction itself by balancing the isobutanol pathway; it is not a mere extra element.

Fifth, Butamax argues that the district court relied too heavily on extrinsic evidence. In cases involving the interpretation of art-specific terms, analyzing

extrinsic evidence is entirely proper. *Serio-US Indus., Inc. v. Plastic Recovery Techs. Corp.*, 459 F.3d 1311, 1319 (Fed. Cir. 2006). As the district court explained:

> The court recognizes that extrinsic evidence generally is not considered in the claim construction exercise. Under the circumstances at bar, however, where the parties are disputing how those of skill in the art would interpret the definition provided by the patentees, the court finds it instructive, if not imperative, to consider expert testimony and the scientific literature referenced in the patent to illuminate the disputed language.

(A15 n.6.)

Finally, Butamax argues that the word "an" in "using NADPH ... as an electron donor" should be construed as "one or more." Butamax's argument is a non-sequitur. Interpreting "an" as "one or more" would render that phrase nonsensical, reading "using NADPH ... as one or more electron donors." Moreover, even if the "one or more" presumption were applicable here, which it is not, it would be overridden by the vast weight of intrinsic and extrinsic evidence supporting the district court's construction. *See Harari v. Lee*, 656 F.3d 1331, 1341-42 (Fed. Cir. 2011).

B. Gevo Does Not Infringe Literally or Under the Doctrine of Equivalents.

1. Butamax stipulated that Gevo does not literally infringe under the district court's construction.

Butamax has stipulated that it cannot prove literal infringement under the district court's construction. (A10758-62.) Accordingly, to the extent the Court affirms the substance of the district court's construction, it should affirm the judgment of no literal infringement as well.

2. The district court correctly granted summary judgment of noninfringement under the doctrine of equivalents.

a. Butamax's equivalents theory fails as a matter of law.

The district court properly granted summary judgment of noninfringement under the doctrine of equivalents. (A40-41.) On appeal, Butamax makes four arguments, none of which shows reversible error. Butamax first argues that the NADPH and NADH "cofactors are not elements of the independent claims." (BM Br. at 60.) That argument is mistaken, because "using NADPH" is a key limitation under the proper construction.[22]

Butamax next points to the function-way-result test, but does not raise a legally cognizable theory, because its proposed function and way are the same—

[22] Butamax also argues that the district court went beyond the briefing in granting summary judgment. (BM Br. at 60.) To the contrary, the arguments the district court addressed came directly from Butamax's own briefing. (*See, e.g.*, A41.)

the function is "donat[ing] a hydride" and the way is "hydride transfers." (BM Br. at 62-63.)

Instead, the undisputed facts show that, by reversing the cofactor dependence from NADPH to NADH, Gevo has dramatically changed the "way" the enzyme works. Because Butamax's equivalents theory would vitiate the "using NADPH" claim requirement—Gevo's bioengineered enzymes use NADH, not NADPH—summary judgment is appropriate. (A41 (citing *Novartis Pharms. Corp. v. Eon Labs Mfg., Inc.*, 363 F.3d 1306, 1312 (Fed. Cir. 2004).)

Moreover, Gevo's change in the "way" also radically alters the "results." The undisputed facts establish that an NADH-dependent KARI enzyme dramatically increases isobutanol yield. (*See supra* § IV.C; A8794 ¶ 6.) *Stumbo v. Eastman Outdoors, Inc.*, 508 F.3d 1358, 1364-65 (Fed. Cir. 2007) (affirming summary judgment of noninfringement under the doctrine of equivalents where the accused product achieved better safety results).

Butamax also argues that the district court's decision on literal infringement necessarily required it also to deny the equivalents motion. Butamax's argument fails because the district court's analysis addressed different questions. The literal infringement question addressed whether undisputed facts showed that Gevo's KARI enzymes were NADPH-dependent. The equivalents question addressed whether the difference between NADH-dependent and NADPH-dependent

enzymes is substantial. Finding disputed issues on one question does not logically entail finding disputed issues on the other.

Finally, Butamax quotes its expert's statement that "'[a] well regarded textbook in the field describes the differences between' NADPH and NADH 'as 'trivial' in chemical terms.'" (BM Br. at 65.) That citation misrepresents the textbook, which states: "The difference between NADH and NADPH is trivial in chemical terms, ***but it is crucial for their distinctive functions***." (A18247.) A conclusory partial quotation taken out of context does not raise a triable issue, even when offered by an expert. (*See* A41 (citing *Zelinski v. Brunswick Corp.*, 185 F.3d 1311, 1317 (Fed. Cir. 1999)).)

As the district court properly held, no reasonable jury could conclude that Gevo's NADH-dependent KARI enzyme is equivalent to the claimed NADPH-dependent AAIR enzyme.

b. The doctrine of prosecution history estoppel bars Butamax's equivalents theory.

As an alternative grounds for affirmance, prosecution history estoppel bars Butamax's equivalents theory. *Spectrum Int'l, Inc. v. Sterilite Corp.*, 164 F.3d 1372 (Fed. Cir. 1998).[23] When a patent applicant responds to patentability "rejection[s] by narrowing his claims, this prosecution history estops him from

[23] Gevo raised the prosecution history estoppel issue in its cross-motion for summary judgment. (A10137-40.)

later arguing that the subject matter covered by the original, broader claim was nothing more than an equivalent." *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabuskiki Co. Ltd.*, 535 U.S. 722, 727 (2002).

This case is a paradigmatic example of prosecution history estoppel. (*See supra* § IV.B.) During prosecution of both the '188 and '889 patents, Butamax originally sought claims to microorganisms expressing an isobutanol pathway without any recited enzyme limitations. (A5874; A7541.) The Patent Office rejected these originally unbounded claims for lack of written description and enablement under 35 U.S.C. § 112. (A6924-25; A7570-74.) Butamax responded to the rejections by amending the claims to limit their scope to the "specific enzymes" described in the specification. (A7094; A7583.) These specific enzymes included express definitions with particular cofactor limitations.

These narrowing amendments were made to overcome rejections directly related to which enzymes would be covered by the claims. Because the amendments were not merely "tangential" to patentability or the now-asserted equivalents, prosecution history estoppel bars Butamax's current litigation efforts to sweep in enzymes other than the "specific enzymes" recited in the specification. *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 457 F.3d 1293, 1314-15 (Fed. Cir. 2006) (rejecting argument that amendment was tangential); *Ranbaxy Pharms., Inc. v. Apotex, Inc.*, 350 F.3d 1235, 1240-41 (Fed. Cir. 2003) (same).

3. Butamax has not shown a basis for summary judgment of infringement even under its proposed constructions.

Butamax argues that not only should the Court adopt its proposed constructions, it should also enter summary judgment of infringement. Butamax, however, has shown no basis for summary judgment in its favor. For example, Butamax has failed to show that Gevo's NADH-dependent KARI uses any *in vivo* detectable levels of NADPH within the accused recombinant microorganisms. Even as to Butamax's *in vitro* tests of Gevo's enzymes outside the organisms, Gevo also presented disputed issues of fact as to the reliability of that testing. (A10180-82 at ¶¶ 63-67.) In addition, as Butamax's experts conceded, Butamax has no evidence that Gevo's yeast use the "contiguous" pathway construction adopted by the district court (which is not presently on appeal). (A18388-89, 179:18-181:14, 182:2-183:19; A18310, 87:16-88:8.)

Accordingly, even if the Court were to adopt either of Butamax's proposed constructions, which it should not, the Court would need to remand to the district court to consider in the first instance the disputed issues of fact raised by Gevo.

C. The District Court Correctly Held that '889 Claims 12 and 13 Are Invalid for Insufficient Written Description.

The district court also correctly held that claims 12 and 13 of the '889 patent are invalid for lack of written description.[24] Butamax bases its written description

[24] Gevo agrees with Butamax that the district court's grant of summary judgment

appeal on the slenderest of disclosures, then improperly tries to fill the void with evidence from outside the "four corners of the specification." (BM Br. at 65-70.) *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc).

Claim 12 recites the "recombinant yeast microorganism of claim 1" further comprising "inactivated genes thereby reducing yield loss from competing pathways for carbon flow." Claim 13 depends from claim 12, and adds the limitation requiring the inactivation of genes that "reduce pyruvate decarboxylate activity" (PDC).

The district court's holding is supported by (1) the lack of disclosure of even a single inactivated gene, much less any teaching on how to inactivate genes to reduce yield loss,[25] and (2) the fact that Butamax needed to supplement its subsequent patent application with extensive disclosure of PDC knockouts to support claims directed to the same subject matter as claims 12 and 13.[26] These deficiencies cannot be cured by either the Dickinson reference or the misconstrued testimony of Gevo's expert. (*See generally* A18039-43 at ¶¶ 190-201.)

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of non-enablement is a scrivener's error, as Gevo did not move for summary judgment on that ground. Butamax's requested relief of reversal, however, is improper. This Court should vacate that part of the district court's judgment, not reverse it.

[25] A18039-41 at ¶¶ 190-95.

[26] A18041 at ¶ 196.

1. The '889 patent disclosure provides no more than a wish or plan to inactivate competing pathways.

Butamax cites four excerpts from the '889 patent as purportedly showing that the patent discloses the invention of inactivating competing pathways. Butamax first cites a sentence stating: "The microbial host also has to be manipulated in order to inactivate competing pathways for carbon flow by deleting various genes." ('889 patent, 16:55-57).) This single sentence identifies no competing pathways or specific genes that could be inactivated to achieve this vague, aspirational reduction in yield loss and provides no examples. (A18039 at ¶ 190.) Such "[a] 'mere wish or plan' for obtaining the claimed invention is not adequate written description." *Centocor Ortho Biotech, Inc. v. Abbott Labs*, 636 F.3d 1341, 1348 (Fed. Cir. 2011); *Ariad Pharm.*, 598 F.3d at 1350 (citing *Fiers v. Revel*, 984 F.2d 1164, 1170 (Fed. Cir. 1993)).

Butamax's argument that this sentence provides "verbatim support in the specification for claim 12" is misplaced under this Court's precedent. (BM Br. at 67.) *Boston Scientific Corp. v. Johnson & Johnson*, 647 F.3d 1353, 1364 (Fed. Cir. 2011) (sole mention of macrocyclic lactone analogs of rapamycin in specification insufficient written description of the genus of macrocyclic lactone analogs). As this Court recognized in *Ariad*: "[G]eneric claim language appearing *in ipsis verbis* in the original specification does not satisfy the written description requirement if it fails to support the scope of the genus claimed .... [A] claim does

not become more descriptive by its repetition ...." *Ariad Pharm.*, 598 F.3d at 1350 (citations omitted).

Butamax's second cited sentence likewise expresses only a legally irrelevant wish: "There is a need ... for an environmentally responsible, cost-effective process for the production of isobutanol as a single product." ('889 patent, 1:63-1:65.) Unrebutted expert testimony established that the patents provide no example of achieving production of isobutanol as a single product, much less doing so by inactivating a specific competing gene. (A18037-38 at ¶¶ 188-89.)

Butamax next cites the discussion of pyruvate decarboxylase in the '889 written description. ('889 patent, 12:12-15; A00054.) As experts for both parties testified, this sentence does not describe a recombinant yeast microorganism with *inactivated* genes to reduce yield loss or PDC activity. (A18040-41, A18042-43 at ¶¶ 193-94, 199; A4427-28, 287:9-18, 291:8-11.) Instead, the excerpt simply acknowledges that pyruvate decarboxylase is one type of decarboxylase enzyme that can convert α-ketoisovalerate to isobutyraldehyde. ('889 patent, 12:12-15.)

Lastly, Butamax cites the Dickinson publication from the background section of the patent. (A17902-07.) Dickinson is irrelevant, because it was not incorporated by reference into the patent. 37 CFR 1.57(b)(1) (references are incorporated into patents only when the perfecting words "incorporated by reference" or similar language is used); *In re de Seversky*, 474 F.2d 671 (CCPA

1973). Even if it were proper to consider Dickinson, the district court correctly found that the reference did not create an issue of fact. Butamax cited the reference in the "Background of The Invention" only to distinguish it. Butamax never relied on that reference to support the description of any Butamax invention. ('889 patent, 1:39-62.) Moreover, as the district court properly noted, Dickinson shows only the unpredictability of this art, stating that "elimination of pyruvate decarboxylase activity in a ... triple mutant *virtually abolished [isobutanol] production*." (A17902 (emphasis added); A00054; A18039-40 at ¶ 192.)

In connection with Dickinson, Butamax also argues that PDC knockout was well-known in the prior art before Butamax's purported invention. Butamax's argument is irrelevant because an expert declaration or prior art publication cannot take the place of an adequate description. *Boston Scientific*, 647 F.3d at 1362-66. In *Boston Scientific*, the court noted a "sole mention" of macrocyclic lactones, the lack of any examples or guidance on how to properly determine whether a compound is a macrocyclic lactone analog of rapamycin, and the unpredictability of the field. *Id.* at 1364. Similarly here, the '889 patent includes only cursory passages related to gene inactivation, recites no examples, and does not purport to solve any of the issues in this unpredictable field.

Accordingly, neither the passages from the '889 patent cited by Butamax nor the Dickinson reference provide any evidence that the inventors had possession of

any inactivated genes, generally or PDC-knockout specifically. *Billups-Rothenberg, Inc. v. Associated Reg'l and Univ. Pathologists, Inc.*, 642 F.3d 1031, 1032 (Fed. Cir. 2011) (claims covering genus of genetic mutations were inadequately described when the patent did not disclose a single species within the genus).

2. The Stephanopoulos testimony is irrelevant.

Butamax also cites several passages from the deposition of Gevo's expert, Dr. Stephanopoulos. This testimony is irrelevant, because it merely shows his recognition that the '889 patent includes only a wish or plan, not an adequate description. For example, Butamax quotes a positive response to the question: "Well, does it tell you ***want*** to delete PDC?" (BM Br. at 68 (emphasis added).) Whether a person of skill would *want* to delete PDC is irrelevant to the legally operative question of whether that person of skill would objectively view the '889 patent as having described the patentees as having possessed such an invention.

Similarly, the statement about producing isobutanol as a "single product" likewise expresses no more than a wish; as discussed above, the patent never discloses any embodiment that would accomplish that result. (A18042-43 at ¶¶ 197-201.) The unrebutted testimony established that making such a modified microorganism would require extensive experimentation, with a low expectation of success because PDC-null yeast are not stable enough to be transformed with a

recombinant biosynthetic pathway and cannot grow on glucose alone. (*Id.*) As in *Boston Scientific*, the existing knowledge in the art cannot excuse the failure to include the disclosure required to show possession of a claimed invention. *Boston Scientific*, 647 F.3d at 1364.

3. Butamax's subsequent patent applications showcase the '889 patent's insufficient description.

Finally, the fact that Butamax's inventors did not have possession of claims 12 and 13 of the '889 patent at the time of the patent application is most starkly illustrated by Butamax's later filed patent application, which sought claims to yeast microorganisms including PDC inactivation. (*See* A17908-47 (material not in the '889 specification highlighted for emphasis).)

The later Butamax application is a continuation-in-part of the '188 and '889 patents and provides extensive disclosure of the rationale for pathway inactivation, details of the pathways to be inactivated, and experiments for preparing a PDC-knockout yeast. (A18041 at ¶ 196.) The detail in this later application stands in sharp contrast to the '889 patent, demonstrating that the '889 patent does not show possession of claims 12 and 13 when the application leading to the '889 patent was filed. *Billups-Rothenberg*, 642 F.3d at 1036 (written description doctrine prevents patentees from "preempt[ing] the future before it arrives"); *Ariad Pharm.*, 598 F.3d at 1352-53 (written description is insufficient where it leaves to others "to complete an unfinished invention").

In fact, the Patent Office has specifically concluded that the '889 patent does not teach the inactivation of PDC genes as recited in Claim 13. During the prosecution of Gevo's own patent application related to PDC, the Examiner considered the '889 patent as potential prior art and concluded that the '889 patent "do[es] not teach the disruption of endogenous pyruvate decarboxylase genes." (A17353.)[27]

Accordingly, the district court correctly concluded that claims 12 and 13 were not adequately described.

VIII. CONCLUSION

For the foregoing reasons, the judgment of noninfringement and invalidity should be affirmed.

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[27] This conclusion has been repeated by the PTO. (A17376.)

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CERTIFICATE OF SERVICE

I hereby certify that on July 19, 2013, true and correct copies of the foregoing **CORRECTED NON-CONFIDENTIAL APPELLEE'S RESPONSIVE BRIEF** were served via ECF as well as via email, on the following:

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July 19, 2013 */s/ Michelle S. Rhyu*

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